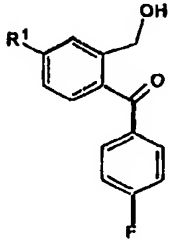




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification : Not classified</p>	A2	<p>(11) International Publication Number: WO 98/19511</p> <p>(43) International Publication Date: 14 May 1998 (14.05.98)</p>		
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> <p>(21) International Application Number: PCT/DK97/00511</p> <p>(22) International Filing Date: 10 November 1997 (10.11.97)</p> <p>(71) Applicant (for all designated States except US): H. LUNDBECK A/S [DK/DK]; Ottiliavej 9, DK-2500 Valby-Copenhagen (DK).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): PETERSEN, Hans [DK/DK]; Guldagervej 11, DK-2720 Vanløse (DK). BØGESØ, Klaus, Peter [DK/DK]; Hørsholm Park 16, 2TV, DK-2970 Hørsholm (DK). BECH SOMMER, Michael [DK/DK]; Aldershvilevej 23 A, DK-2880 Bagsvaerd (DK).</p> <p>(74) Common Representative: H. LUNDBECK A/S; MEI-DAHL PETERSEN, John, Ottiliavej 9, DK-2500 Valby-Copenhagen (DK).</p> </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>Before the expiration of the time limit referred to in Article 21(2)(a) on the request of the applicant. Without international search report and to be republished upon receipt of that report. Without classification; title and abstract not checked by the International Searching Authority.</i></p> </td> </tr> </table>			<p>(21) International Application Number: PCT/DK97/00511</p> <p>(22) International Filing Date: 10 November 1997 (10.11.97)</p> <p>(71) Applicant (for all designated States except US): H. LUNDBECK A/S [DK/DK]; Ottiliavej 9, DK-2500 Valby-Copenhagen (DK).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): PETERSEN, Hans [DK/DK]; Guldagervej 11, DK-2720 Vanløse (DK). BØGESØ, Klaus, Peter [DK/DK]; Hørsholm Park 16, 2TV, DK-2970 Hørsholm (DK). BECH SOMMER, Michael [DK/DK]; Aldershvilevej 23 A, DK-2880 Bagsvaerd (DK).</p> <p>(74) Common Representative: H. LUNDBECK A/S; MEI-DAHL PETERSEN, John, Ottiliavej 9, DK-2500 Valby-Copenhagen (DK).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>Before the expiration of the time limit referred to in Article 21(2)(a) on the request of the applicant. Without international search report and to be republished upon receipt of that report. Without classification; title and abstract not checked by the International Searching Authority.</i></p>
<p>(21) International Application Number: PCT/DK97/00511</p> <p>(22) International Filing Date: 10 November 1997 (10.11.97)</p> <p>(71) Applicant (for all designated States except US): H. LUNDBECK A/S [DK/DK]; Ottiliavej 9, DK-2500 Valby-Copenhagen (DK).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): PETERSEN, Hans [DK/DK]; Guldagervej 11, DK-2720 Vanløse (DK). BØGESØ, Klaus, Peter [DK/DK]; Hørsholm Park 16, 2TV, DK-2970 Hørsholm (DK). BECH SOMMER, Michael [DK/DK]; Aldershvilevej 23 A, DK-2880 Bagsvaerd (DK).</p> <p>(74) Common Representative: H. LUNDBECK A/S; MEI-DAHL PETERSEN, John, Ottiliavej 9, DK-2500 Valby-Copenhagen (DK).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>Before the expiration of the time limit referred to in Article 21(2)(a) on the request of the applicant. Without international search report and to be republished upon receipt of that report. Without classification; title and abstract not checked by the International Searching Authority.</i></p>			
<p>(54) Title: METHOD FOR THE PREPARATION OF CITALOPRAM</p> <div style="text-align: center; margin: 20px 0;">  <p style="margin-top: 10px;">(IV)</p> </div> <p>(57) Abstract</p> <p>A method for the preparation of citalopram is described comprising reduction of the oxo group of a compound of formula (IV), wherein R¹ is CN, C₁₋₆ alkyloxycarbonyl or C₁₋₆ alkylaminocarbonyl, ring closure of the resulting hydroxy compound thereby obtaining the corresponding 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran, then if R¹ is cyano using it directly in the next step and if R¹ is C₁₋₆ alkyloxycarbonyl or C₁₋₆ alkylaminocarbonyl, conversion of the compound to the corresponding compound wherein R¹ is cyano; and alkylation of the resulting 5-cyano compound with 3-dimethyl-aminopropylhalogenid in basic conditions thereby obtaining citalopram.</p>				

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

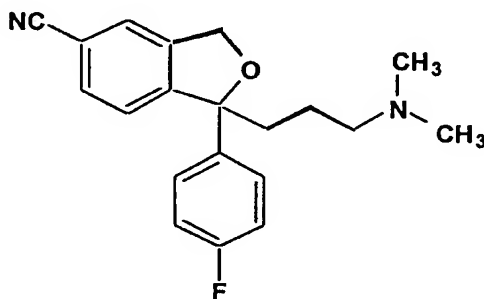
AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Method for the Preparation of Citalopram

The present invention relates to a method for the preparation of the well known antidepressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile.

Background of the Invention.

Citalopram is a well known antidepressant drug that has now been on the market for some years and has the following structure:



Formula I

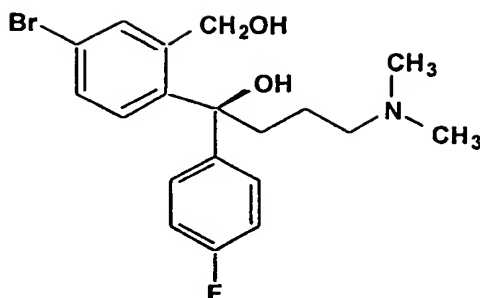
It is a selective, centrally active serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel, *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, 1982, 6, 277-295 and A. Gravem, *Acta Psychiatr. Scand.*, 1987, 75, 478-486. The compound has further been disclosed to show effects in the treatment of dementia and cerebrovascular disorders, EP-A 474580.

Citalopram was first disclosed in DE 2,657,271 corresponding to US 4,136,193. This patent publication describes the preparation of citalopram by one method and outlines a further method which may be used for preparing citalopram.

According to the process described, the corresponding 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile is reacted with 3-(N,N-dimethylamino)propyl-chloride in the presence of methylsulfinylmethide as condensing agent. The starting material was prepared from the corresponding 5-bromo derivative by reaction with cuprous cyanide.

According to the method, which is only outlined in general terms, citalopram may be obtained by ring closure of the compound:

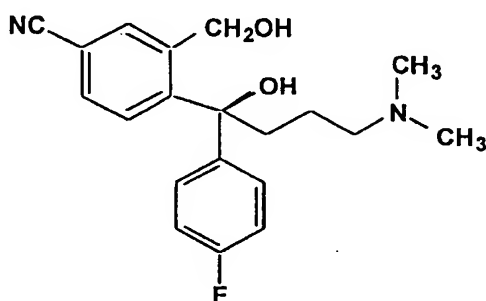
CONFIRMATION COPY



Formula II

in the presence of a dehydrating agent and subsequent exchange of the 5-bromo group with cuprous cyanide. The starting material of Formula II is obtained from 5-bromophthalide by two successive Grignard reactions, i.e. with 4-fluorophenyl magnesium chloride and N,N-dimethylaminopropyl magnesium chloride, respectively.

A new and surprising method and an intermediate for the preparation of citalopram were described in US Patent No 4,650,884 according to which an intermediate of the formula



Formula III

is subjected to a ring closure reaction by dehydration with strong sulfuric acid in order to obtain citalopram. The intermediate of Formula III was prepared from 5-cyanophthalide by two successive Grignard reactions, i.e. with 4-fluorophenyl magnesium halogenide and N,N-dimethylaminopropyl magnesium halogenide, respectively.

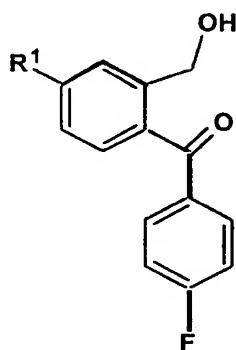
Finally, methods of preparing the individual enantiomers of citalopram are disclosed in US Patent No 4,943,590 from which it also appears that the ring closure of the intermediate of Formula III may be carried out via a labile ester with a base.

It has now, surprisingly, been found that citalopram may be manufactured by a novel favourable and safe procedure using convenient starting materials.

Summary of the invention

Accordingly, the present invention relates to a novel method for the preparation of citalopram comprising the steps of :

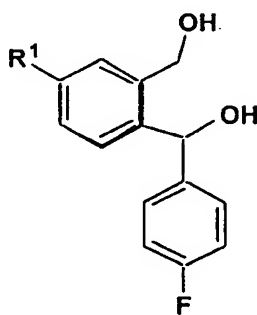
a) reduction of a compound of Formula IV



Formula IV

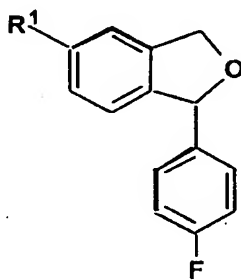
wherein R¹ is CN, C₁₋₆ alkyloxycarbonyl or C₁₋₆ alkylaminocarbonyl,

b) effecting ring closure of the resulting compound of Formula V



Formula V

wherein R¹ is as defined above thereby obtaining a compound of Formula VI

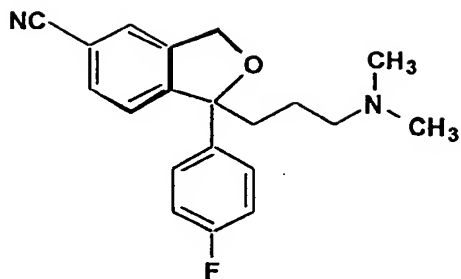


Formula VI

wherein R¹ is as defined above

c) then if R¹ is cyano using the compound of Formula VI directly in the next step and if R¹ is C₁₋₆ alkyloxycarbonyl or C₁₋₆ alkylaminocarbonyl, converting the compound of Formula VI to the corresponding compound wherein R¹ is cyano; and

d) alkylating the resulting 5-cyano compound of formula VI (R¹ = CN) with 3-dimethylaminopropylhalogenid in basic conditions thereby obtaining citalopram,



Formula I

which is isolated as the base or a pharmaceutically acceptable salt thereof.

- 5 In another aspect, the present invention provides the novel intermediates of Formula V.

A further aspect of the invention relates to the novel intermediate for preparation of citalopram of Formula VI wherein R¹ is C₁₋₆ alkylloxycarbonyl or C₁₋₆ alkylaminocarbonyl.

- 10 In yet another aspect, the present invention relates to an antidepressant pharmaceutical composition comprising citalopram manufactured by the process of the invention.

- Throughout the specification and claims, C₁₋₆ alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2,2-dimethyl-1-ethyl and 2-methyl-1-propyl.

The 3-dimethylaminopropylhalogenide used may be the chloride, bromide or iodide, preferably the chloride.

- 20 The reduction of the compound of Formula IV may be performed with any convenient reducing agent, preferably by NaBH₄ in an alcohol, such as ethanol or methanol in basic conditions or with zinc in aqueous acetic acid.

- The ring closure of the compound of Formula V may be effected by an acid or via a labile ester with a base. Acidic ring closure is performed by an inorganic acid, such as a sulfuric or phosphoric acid, or an organic acid, such as methylsulfonic, p-toluenesulfonic or trifluoroacetic acid. The basic ring closure may be performed via a labile ester, such as the methane sulfonyl, p-toluene sulfonyl, 10-camphorsulfonyl, trifluoroacetyl or trifluoromethanesulfonyl ester with addition of a base, such as triethyl amine, dimethylaniline, pyridine, etc. The reaction is performed in an inert solvent, preferably with cooling, in particular about 0 °C and is preferably carried out by a one-pot procedure, i.e. with esterification and simultaneous addition of the base.

When R¹ is an alkylaminocarbonyl group, the conversion to cyano may be performed by conventional nitril synthesis. Thus, the amide of Formula V wherein R¹ is an alkylaminocarbonyl group is preferably converted to the cyano compound, i.e. citalopram, by reaction with a dehydrating agent, most preferably thionyl chloride or phosphor pentachloride.

5

When R¹ is an alkyloxycarbonyl group, the conversion to cyano is preferably performed via the corresponding amide group which is then converted to the cyano group in the same way as compounds of Formula VI wherein R¹ is an alkylaminocarbonyl group.

- 10 The reaction of alkyloxycarbonyl to amide is carried out by hydrolysis with an acid or a base and subsequent conversion to acid chloride and amidation by reaction with ammonia or an alkylamine, preferably t-butyl amine. Acid hydrolysis may be performed by use of any suitable acid, such as HBr, HCl, HBr/acetic acid. Basic hydrolysis may be performed with any suitable base, such as K₂CO₃, NaOH, KOH, etc. The conversion to amide may also be
15 obtained by reaction of the ester (R¹ is an alkyloxycarbonyl group) with ammonia or an alkylamine under pressure and heating. The amide obtained is converted to the cyano group as described above.

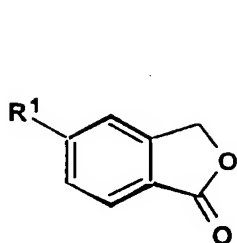
- Alternatively, an ester, i.e. a compound of Formula VI wherein R¹ is an alkyloxycarbonyl
20 group may be hydrolysed and then reacted with chlorosulfonyl isocyanate in order to form the nitrile.

- The alkylation in step d) is carried out by addition of the 3-dimethylaminopropylhalogenide to the compound of formula VI (R¹ = CN) in a proper solvent, such as an ether, preferably
25 1,2-dimethoxyethane (DME), THF, diglyme or diethylether, in the presence of a base, preferably lithiumdiisopropylamine (LDA).

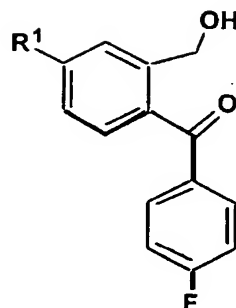
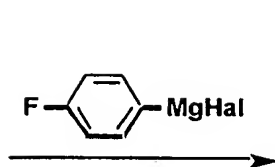
The process of the invention may be carried out with or without isolation of the intermediates.

- 30 Other reaction conditions, solvents, etc. are conventional conditions for such reactions and may easily be determined by a person skilled in the art.

- The starting materials of formula IV may be prepared from the corresponding phthalide compound by reaction with a Grignard reagent of 4-halogen-fluorophenyl as exemplified
35 with the magnesiumhalogenide in the following reaction scheme:



Formula VII



Formula IV

wherein R¹ is as defined above.

When R¹ is a cyano group, the starting materials of formula VII may be prepared as described
 5 in Tirouflet, J.; Bull.Soc.Sci. Bretagne 26, 1959,35.

Other starting materials of formula IV may be prepared from 5-carboxyphtalide by reaction
 with thionyl chloride and then C₁₋₆ alkanol or C₁₋₆ alkylamine. 5-carboxyphtalide is
 commercially available and may be prepared by well known procedures (Tirouflet, J.;
 10 Bull.Soc.Sci. Bretagne 26, 1959,35).

In a preferred embodiment of the invention, R¹ is cyano.

In another embodiment of the invention, R¹ is C₁₋₆ alkyloxycarbonyl, the C₁₋₆ alkyl group
 15 being preferably ethyl, propyl, or butyl, preferably ethyl, 2-propyl or t-butyl.

In yet another embodiment of the invention, R¹ is C₁₋₆ alkylaminocarbonyl, the C₁₋₆ alkyl
 group being preferably ethyl, propyl, or butyl, preferably ethyl, 2-propyl or t-butyl, most
 preferably t-butyl.

20

The compound of general Formula I may be used as the free base or as a pharmaceutically
 acceptable acid addition salt thereof. As acid addition salts, such salts formed with organic or
 inorganic acids may be used. Exemplary of such organic salts are those with maleic, fumaric,
 benzoic, ascorbic, succinic, oxalic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic,
 25 acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic,
 citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene
 sulfonic and theophylline acetic acids, as well as the 8-halothephyllines, for example 8-
 bromothephylline. Exemplary of such inorganic salts are those with hydrochloric,
 hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

30

The acid addition salts of the compounds may be prepared by methods known in the art. The
 base is reacted with either the calculated amount of acid in a water miscible solvent, such as

acetone or ethanol, with subsequent isolation of the salt by concentration and cooling, or with an excess of the acid in a water immiscible solvent, such as ethylether, ethylacetate or dichloromethane, with the salt separating spontaneously.

- 5 The pharmaceutical compositions of the invention may be administered in any suitable way and in any suitable form, for example orally in the form of tablets, capsules, powders or syrups, or parenterally in the form of usual sterile solutions for injection.

The pharmaceutical formulations of the invention may be prepared by conventional methods
10 in the art. For example, tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tableting machine. Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive colourings, aroma, preservatives etc. may be used provided that they are compatible
15 with the active ingredients.

Solutions for injections may be prepared by solving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilization of the solution and filling in suitable ampules or vials.

- 20 Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Examples

The invention is further illustrated by the following examples.

25

Example 1

(4-Cyano-2-hydroxymethylphenyl)(4-fluorophenyl)methanol.

- A solution of 4-fluorophenylmagnesium bromide, prepared from 4-fluorobromobenzene (605 g, 3.45 mole) and magnesium turnings (107 g, 4.4 mole) in dry THF (1200 mL), is added
30 dropwise to a suspension of 5-cyanophthalid (500 g, 3.14 mole) in dry THF (3000 mL). The temperature is kept below 5 °C. After the addition is complete, the reaction mixture is stirred the night over at room temperature.

Ethanol (4500 mL) is added to the reaction mixture and NaBH₄ (238 g, 6.30 mole) is added to the mixture in portions of 50 grams and is stirred the night over at room temperature.

- 35 About 2/3 of the solvents is removed *in vacuo* and water (4000 mL) is added to the reaction mixture. The resulting solution is extracted with EtOAc (2x500 mL). Evaporation of the solvents leaves a crude title compound (780 g) as an oil which is deemed pure enough for further reaction.

A pure sample is obtained after column chromatography on silica gel using EtOAc/n-Hep-
tane (1/1) as eluent. The title compound is obtained as crystals after evaporation of the eluent.
DSC onset: 116.5 °C.

¹H NMR (DMSO-d₆, 500 MHz): 4.42 (1H, dd J=13 Hz, J=5 Hz), 4.53 (1H, dd J=13 Hz, J=5
5 Hz), 5.45 (1H, t J=5 Hz), 5.98 (1H, d J=3 Hz), 6.14 (1H, d J=3 Hz), 7.15 (2H, t J=10 Hz),
7.35 (2H, m), 7.74 (1H, d J=8.5 Hz), 7.77 (1H, d J=8.5 Hz), 7.83 (1H, s).

Anal. calcd. for C₁₅H₁₂N₁F₁O₂; C, 70.02; H, 4.71; N, 5.45. Found C, 70.01; H, 4.71; N, 5.51.

1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.

10 Crude (4-cyano-2-hydroxymethylphenyl)(4-fluorophenyl)methanol (700 g) is dissolved in
H₃PO₄ (60%, 3000 mL) and the solution is heated to 80 °C for 3 hours. Toluene (1000 mL) is
added and the phases are separated. The aqueous phase is further extracted with toluene
(1000 mL). The toluene phases are joined and the solvents are removed *in vacuo*. The re-
maining crystals are recrystallized from EtOH (99%). Yield 219 g (29%). DSC onset: 97 °C.

15 ¹H NMR (DMSO-d₆, 500 MHz): 5.15 (1H, d J=12.5 Hz), 5.32 (1H, d J=12.5 Hz), 6.27 (1H,
s), 7.21 (2H, t J=10 Hz), 7.25 (1H, d J=8.5 Hz), 7.40 (2H, m), 7.71 (1H, d J=8.5 Hz), 7.90
(1H, s).

Anal. calcd. for C₁₅H₁₀N₁F₁O₁; C, 75.30; H, 4.22; N, 5.86. Found C, 75.01; H, 4.22; N, 5.83.

20 *1-(3-Dimethylaminopropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.*
n-BuLi (1.6 N in hexane, 320 mL) is added to diisopropylamine (55 g, 0.5 mole) dissolved in
DME (150 mL) at - 50 °C over a nitrogen atmosphere. 1-(4-fluorophenyl)-1,3-dihydroiso-
benzofuran-5-carbonitrile (62 g, 0.26 mole) is dissolved in DME (500 mL) and added
dropwise while the temperature is kept below - 40° C. After addition (45 min), the dark red
25 solution is stirred for an additional period of 20 min. 3-Dimethylpropylchloride (100 g, 0.82
mole) is added in one portion at - 50 °C and the cooling is removed. After 60 min, the
solution is warmed to 50 °C for 120 min. The reaction mixture is poured onto ice water (1 L)
and extracted with toluene (2x500 mL). The organic phase is extracted with HCl (4 N, 500
mL). The acid solution is made alkaline (pH = 10) with NaOH (10 N) and extracted with
30 toluene (500 mL) which is washed with water (3x200 ml). The toluene phase is dried
anhydrous Na₂SO₄ (50 g), treated with active carbon and the solvents are removed *in vacuo*.
The title compound (64-71 g, 76-84%) is obtained as an oil.

¹H NMR (DMSO-d₆, 500 MHz): 1.20 (1H, m), 1.30 (1 H, m), 2.00 (6H, s), 2.10-2.20 (4H,
m), 5.12 (1H, d, J=13.5 Hz), 5.20 (1H, d, J=13.5 Hz), 7.13 (2H, t, J=8.5 Hz), 7.58 (2H, dt,
35 J=1.2 Hz J=8.5 Hz), 7.70-7.78 (3H, m).

The oxalic acid salt is crystallized from acetone. DSC onset: 156 °C. Anal. calcd. for
C₂₂H₂₃N₂F₁O₅; C, 63.75; H, 5.60; N, 6.76. Found C, 61.60; H, 5.62; N, 6.63.

Eksample 2*(4-Ethoxycarbonyl-2-hydroxymethylphenyl)(4-fluorophenyl)methanol.*

A solution of 4-fluorophenylmagnesium bromide, prepared from 4-fluorobromobenzene (21 g, 0.12 mole) and magnesium turnings (3.4 g, 0.14 mole) in dry THF (150 ml), is added
5 dropwise to a suspension of 5-ethoxycarbonylphthalide (20.6 g, 0.1 mole) in dry THF (150 ml). The temperature is kept below 5 °C. After the addition is complete, the reaction mixture is stirred the night over at room temperature.

Ethanol (300 ml) is added to the reaction mixture and NaBH₄ (7.6 g, 0.2 mole) is added to the mixture in portions of about 1 gram and is stirred for 4 hours at room temperature.

10 The solvents are removed *in vacuo* and ammonium chloride (sat. aq, 300 ml) is added to the remaining oil. The pH of the resulting solution is adjusted to 7.2 with aqueous 4 N HCl and extracted with EtOAc (2x100 ml). Evaporation of the solvents leaves a crude title compound as an oil (30 g) which is deemed pure enough for further reaction.

¹H NMR (DMSO-d₆, 500 MHz): 1.3 (3H, t J=7 Hz), 4.3 (2H, d J=7Hz), 4.35-4.5 (2H, m),
15 4.55-4.65 (2H, m) 5.35 (1H, t J=3Hz) 5.95 (1H, d J=3 Hz), 6.05 (1H, d J=3 Hz), 7.13 (2H, t J=10Hz), 7.33 (2H, m), 7.64 (1H, d J=8.5 Hz),), 7.90 (1H, d J=8.5 Hz), 8.10 (1H, s).

Ethyl 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carboxylat.

Crude (4-ethoxycarbonyl-2-hydroxymethylphenyl)(4-fluorophenyl)methanol (30 g) is
20 dissolved in H₃PO₄ (60%, 250 ml) and the solution is heated to 80°C for 1.5 hours. Water (300 ml) and EtOAc (100 ml) is added and the phases are separated. The aqueous phase is further extracted with EtOAc (100 ml). The organic phases are joined and the solvents are removed *in vacuo*. The yield of the remaining somewhat impure oil is 30 g.

¹H NMR (DMSO-d₆, 500 MHz): 1.3 (3H, t J=7 Hz), 4.3 (2H, d J=7Hz), 5.17 (1H, d J=13
25 Hz), 5.35 (1H, d J=13 Hz), 6.25 (1H, s) 7.20 (3H, d+t J=8.5Hz J=10 Hz), 7.41 (2H, m), 7.86 (1H, d J=8.5 Hz), 7.97 (1H, s).

1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carboxylic acid.

Crude ethyl 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carboxylat (30 g) is dissolved in
30 EtOH (96%, 150 ml) and aqueous 2N NaOH (150 ml). The solution is refluxed for 1 hour. 1/2 of the volume is removed *in vacuo*. The aqueous phase is extracted with EtOAc (2x100 ml). The aqueous phase is made acidic (pH=1, conc. HCl) and after cooling to 5 °C the white crystals are filtered off. Yield 16g. Overall yield is 66% starting from 5-ethoxycarbonyl-phthalid. Mp 187-190 °C.

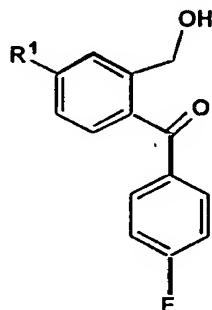
35 ¹H NMR (DMSO-d₆, 500 MHz) 5.15 (1H, d J=13 Hz), 5.33 (1H, d J=13 Hz), 6.23 (1H, s) 7.18 (3H, d+t J=8.5Hz J=10 Hz), 7.40 (2H, m), 7.84 (1H, d J=8.5 Hz), 7.94 (1H, s) 12.95 (1H, bs).

The compound obtained is then converted to the corresponding cyano compound which again is alkylated as described in Example 1.

CLAIMS

1. A method for the preparation of citalopram comprising the steps of

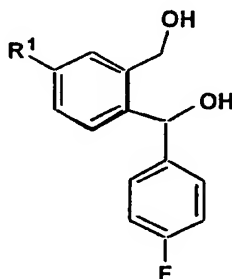
5 a) reduction of a compound of Formula IV



Formula IV

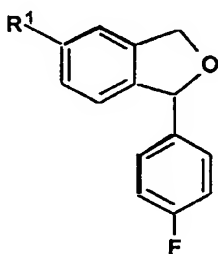
wherein R^1 is CN, C_{1-6} alkyloxycarbonyl or C_{1-6} alkylaminocarbonyl,

b) effecting ring closure of the resulting compound of Formula V



Formula V

wherein R^1 is as defined above thereby obtaining a compound of Formula VI



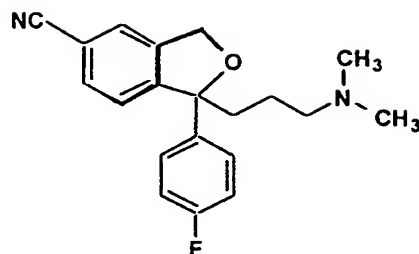
Formula VI

15 wherein R^1 is as defined above;

c) then if R^1 is cyano using the compound of Formula VI directly in the next step and if R^1 is C_{1-6} alkyloxycarbonyl or C_{1-6} alkylaminocarbonyl, converting the compound of Formula VI to the corresponding compound wherein R^1 is cyano; and

d) alkylating the resulting 5-cyano compound of formula VI ($R^1 = \text{CN}$) with 3-dimethyl-aminopropylhalogenid in basic conditions thereby obtaining citalopram,

20



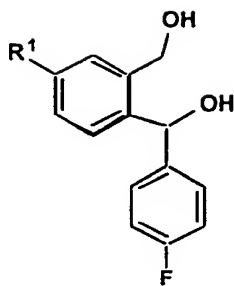
Formula I

which is isolated as the base or a pharmaceutically acceptable salt thereof.

- 5 2. The method of Claim 1 wherein R¹ is CN.
3. The method of Claim 1 wherein R¹ is C₁₋₆ alkyloxycarbonyl.
4. The method of Claim 1 wherein R¹ is C₁₋₆ alkylaminocarbonyl.
- 10 5. The method of Claim 3 or 4 wherein C₁₋₆ alkyl is ethyl-, propyl-, or butyl, preferably ethyl, 2-propyl or t-butyl, most preferably t-butyl.
6. The method of any of Claims 1 - 5 wherein the reduction of the compound of Formula
- 15 IV is performed by use of NaBH₄ in an alcohol, such as ethanol or methanol in basic conditions.
7. The method of any of Claims 1-6 wherein the ring closure of the compound of Formula V is effected by acidic ring closure performed by an inorganic acid, such as a
- 20 sulfuric or phosphoric acid, or an organic acid, such as methanesulfonic, p-toluenesulfonic or trifluoroacetic acid.
8. The method of any of Claims 1-6 wherein the ring closure of the compound of Formula V is performed by a basic ring closure via a labile ester preferably with
- 25 simultaneous esterification and addition of base.
9. The method of Claim 8 wherein the labile ester is the methane sulfonyl, p-toluene sulfonyl, 10-camphorsulfonyl, trifluoroacetyl or trifluoromethanesulfonyl ester and the base is triethyl amine, dimethylaniline or pyridine.
- 30 10. The method of Claim 3 wherein the conversion of the C₁₋₆ alkyloxycarbonyl to cyano is performed via the corresponding amide group.

11. The method of Claim 10 wherein the reaction of C₁₋₆ alkyloxycarbonyl to amide is carried out by hydrolysis with an acid or a base, subsequent conversion to acid chloride and amidation by reaction with ammonia or an alkylamine, preferably t-butyl amine.
- 5 12. The method of Claim 11 wherein the hydrolysis is performed by use of a suitable acid, such as HBr, HCl, HBr/acetic acid.
13. The method of Claim 11 wherein the hydrolysis is performed by use of a suitable base, preferably K₂CO₃, NaOH or KOH.
- 10 14. The method of Claim 8 wherein the reaction of C₁₋₆ alkyloxycarbonyl to amide is carried out by reaction of the ester with ammonia or an alkylamine under pressure and heating.
- 15 15. The method of any of Claims 4 and 9-14 wherein the amide is converted to the cyano group by reaction with a dehydrating agent, preferably thionyl chloride or phosphor pentachloride.
16. The method of any of Claims 1 - 15 wherein the 3-dimethylaminopropylhalogenide used as alkylation agent in step d) is the chloride, bromide or iodide, preferably the chloride.
- 20 17. The method of any of Claims 1 - 16 wherein the alkylation in step d) is carried out in an ether, preferably 1,2-dimethoxyethane, THF, Diglyme or diethylether.
- 25 18. The method of any of Claims 1 - 17 wherein the alkylation in step d) is carried out in the presence of a base, preferably lithiumdiisopropylamine.
19. The method of any of Claims 1 - 18 wherein the starting material of formula IV is prepared from the corresponding phthalide compound by reaction with a Grignard reagent of 4-halogen-fluorophenyl, preferably a 4-fluorophenylmagnesiumhalogenide, most preferably the magnesiumbromide.
- 30 20. The method of Claim 1 wherein R¹ is cyano, the starting material of formula IV is prepared from the corresponding phthalide compound by reaction with a 4-fluorophenylmagnesiumhalogenide, the reduction in a) is performed by NaBH₄ in an alcohol, the ring closure in b) is effected by an inorganic acid and the alkylation in d) is carried out by use of dimethylaminopropylchloride in an ether in the presence of lithiumdiisopropylamine

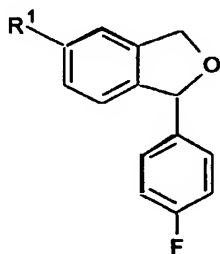
21. A compound of Formula V



Formula V

5 wherein R¹ is CN, C₁₋₆ alkyloxycarbonyl or C₁₋₆ alkylaminocarbonyl.

22. A compound of Formula VI



Formula VI

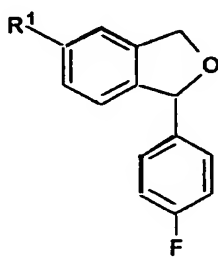
10

wherein R¹ is C₁₋₆ alkyloxycarbonyl or C₁₋₆ alkylaminocarbonyl.

23. An antidepressant pharmaceutical composition comprising citalopram manufactured by the process of any of Claims 1 - 20.

15

24. A method for the preparation of citalopram comprising alkylating a compound of formula VI

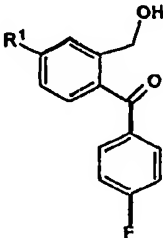


Formula VI

20 wherein R¹ is with 3-dimethyl-aminopropylhalogenid in basic conditions in which the reaction is carried out in an ether, preferably 1,2-dimethoxyethane, THF, diglyme or diethylether, in the presence of lithiumdiisopropylamine.



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 307/87, A61K 31/34	A3	(11) International Publication Number: WO 98/19511 (43) International Publication Date: 14 May 1998 (14.05.98)
(21) International Application Number: PCT/DK97/00511 (22) International Filing Date: 10 November 1997 (10.11.97) (71) Applicant (for all designated States except US): H. LUNDBECK A/S [DK/DK]; Ottiliavej 9, DK-2500 Valby-Copenhagen (DK). (72) Inventors; and (75) Inventors/Applicants (for US only): PETERSEN, Hans [DK/DK]; Guldagervej 11, DK-2720 Vanløse (DK). BØGESØ, Klaus, Peter [DK/DK]; Hørsholm Park 16, 2TV, DK-2970 Hørsholm (DK). BECH SOMMER, Michael [DK/DK]; Aldershvilevej 23 A, DK-2880 Bagsvaerd (DK). (74) Common Representative: H. LUNDBECK A/S; MEI-DAHL PETERSEN, John, Ottiliavej 9, DK-2500 Valby-Copenhagen (DK).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> <i>Before the expiration of the time limit referred to in Article 21(2)(a) on the request of the applicant.</i> (88) Date of publication of the international search report: 6 August 1998 (06.08.98)
(54) Title: METHOD FOR THE PREPARATION OF CITALOPRAM <div style="text-align: center;">  <p>(IV)</p> </div> (57) Abstract <p>A method for the preparation of citalopram is described comprising reduction of the oxo group of a compound of formula (IV), wherein R¹ is CN, C₁₋₆ alkyloxycarbonyl or C₁₋₆ alkylaminocarbonyl, ring closure of the resulting hydroxy compound thereby obtaining the corresponding 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran, then if R¹ is cyano using it directly in the next step and if R¹ is C₁₋₆ alkyloxycarbonyl or C₁₋₆ alkylaminocarbonyl, conversion of the compound to the corresponding compound wherein R¹ is cyano; and alkylation of the resulting 5-cyano compound with 3-dimethyl-aminopropylhalogenid in basic conditions thereby obtaining citalopram.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 97/00511

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 307/87, A61K 31/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Eur. J. Med. Chem. - Chimica Therapeutica, Volume 12, No 3, 1977, Allan J. Bigler et al, "Quantitative structure-activity relationships in a series of selective 5-HT uptake inhibitors" page 289 - page 295	1-22,24
X	--	23
A	US 3467675 A (POVL VIGGO PETERSEN ET AL), 16 Sept 1969 (16.09.69) -----	1-24

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

15 June 1998

Date of mailing of the international search report

26 -06- 1998

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer

Göran Karlsson
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

Information on patent family members

09/06/98

International application No.

PCT/DK 97/00511

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3467675 A	16/09/69	BE 678035 A	19/09/66
		BR 6677980 D	00/00/00
		BR 6677982 D	00/00/00
		CH 475232 A	15/07/69
		CH 491102 A	31/05/70
		CH 495976 A	15/09/70
		DE 1543714 A,B,C	02/01/70
		DE 1543715 A,B,C	02/12/71
		DK 112531 B	23/12/68
		DK 114981 B	25/08/69
		FI 48730 B	02/09/74
		FI 48731 B	02/09/74
		FR 1491369 A	00/00/00
		FR 1491370 A	00/00/00
		GB 1102762 A	00/00/00
		NL 6603603 A	20/09/66
		NL 6603604 A	19/09/66
		NL 6603606 A	20/09/66
		SE 326193 B	20/07/70
		SE 326194 B	20/07/70
